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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/758,033	11/27/1996	GARY L. CLAYMAN	INGN:022	5378

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	08/758,033	CLAYMAN, GARY L.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-14,16-20,26-32,36,37, and 146-150* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-14,16-20,26-32,36,37 and 146-150* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner prosecuting this case has changed. All inquiries directed to the application should be directed to examiner W. - C. Winston Shen.

This application 08/758,033 filed on November 27, 1996 claims benefit of the provisional application 60/007,810 filed on 11/30/1995.

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 21, 2006 has been entered.

Status of claims: Claims 1-9, 11-14, 16-20, 26-32, 36, 37, and 146-150 are currently under examination.

Information Disclosure Statement

2. In compliance with the duty of disclosure under 37 C.F.R. § 1.56, Applicant filed an Information Disclosure Statement (IDS) on November 21, 2006. Reference B5 is crossed out because it is written in French. References B6, B11, B17, B18, B19, B23, B24, B25; C169, C181, C216, and C222 are considered for "Abstract only" because either only abstract is in English or only the abstract from PubMed is submitted in the filed IDS.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-9, 11-14, 16-19, 26, 36, 37, and 146-150 are rejected under 35 U.S.C. 102(e) as being as being anticipated by Xu et al. (Xu et al., U.S. Patent 5,496,731 issued on March 5, 1996; listed as reference A12 in the IDS filed by applicant on Nov. 21, 2006) as evidenced by Fung (U.S. Patent 6,590,086, issued July 8, 2003) and Donehower, 1994 (Tumor suppressor gene p53 and apoptosis, *The Cancer Bulletin* 46: 161-166, 1994; listed as reference C89 in the IDS filed by applicant on Nov. 21, 2006).

Xu et al. teach broad-spectrum tumor suppressor genes, gene products and methods for *tumor suppressor gene therapy* (See title, Xu et al., 1996). The tumor suppressor genes taught by Xu et al. include **p53** (See section 1.3.3.3, column 5, Xu et al., 1996).

Xu et al., teach methods of treating a mammal having a disease or disorder characterized by abnormal cellular proliferation, such as a tumor or cancer and methods of treating abnormally proliferating cells, such as tumor or cancer cells (See abstract, Xu et al., 1996). In a more preferred embodiment the tumor or ***cancer cells are cells having no detectable genetic defect of a tumor suppressor gene --- a p53 gene*** (See lines 30-33 column 11, Xu et al., 2003) -

-- which reads on the limitation of a tumor cell expressing wild-type p53 recited in claim 1 of instant application ---; consistently, Xu et al. further teach that an advantage of the invention by Xu et al. is that *the methods and products herein disclosed* (which reads on expressing functional p53 for treating tumor recited in claim 1 of instant application) *can be used for therapeutic treating* ***tumors having no specific tumor suppressor gene defects***, which provides a significant advantage over previous techniques for human tumor suppressor gene therapy (See lines 22-27, column 15, Xu et al., 1996). Moreover, Xu et al. teach the ***human*** *bladder cancer* represents an ideal model for practicing tumor suppressor gene therapy of solid tumors (See lines 1-2, column 30, Xu et al., 2003), and the treatment of ***human*** *non-small cell lung cancers in vivo* (See lines 64-65, column 30, Xu et al., 1996).

With regard to various tumors (claims 2-5 of instant application), Xu et al. teach benign and malignant tumor (See line 50-51, column 11, Xu et al., 1996), lung carcinoma (line 35, column 11, Xu et al., 1996), and various sarcomas (See Table 1, column 15, Xu et al., 1996).

With regard to routes for administering viral expression vector (step (b) of claim 1, and claims 147-150 of instant application), Xu et al. teach effective concentration of active vectors can be administered topically, intraocularly, *parenterally*, orally, intranasally, *intravenously*, intramuscularly, subcutaneously or by *any other effective means*. In particular, the vector may be *directly injected into a target cancer or tumor tissue* by a needle in amounts effective to treat the tumor cells of the target tissue.

With regard to viral expression construct (claims 6-9, 19 of instant application), Xu et al., teach expression vectors compatible with mammalian host cells for use in genetic therapy of tumor or cancer cells, include, but are not limited to: plasmids, retroviral vectors, adenovirus

vectors, herpes viral vectors, and non-replicative avipox viruses, as disclosed, for example, by U.S. Pat. No. 5,174,993 (See last paragraph, column 16, Xu et al., 1996); and an adenovirus type 5 (Ad5) deletion mutant, Ad-d1324, and a plasmid, pTG5955 (Rosenfeld, M. A., et al., Cell, 1992, 68:143-155) are used to construct an adenovirus vector able to infect mammalian cells and express a tumor suppressor protein under the control of the adenovirus type 2 (Ad2) major late promoter, the CMV promoter, the β-actin promoter or any other effective promoter (See lines 20-27, column 17, Xu et al., 1996). It is noted that an adenovirus type 5(Ad5) deletion mutant harbors deletions at E1 and E3 regions. It is also noted that regarding the p53-encoding ploynucleotide being tagged so that expression of p53 from said expression vector can be detected (claim 19 of instant application), the limitation reads on the selection of the expression vector bearing neo gene, which is indirectly tagged to the p53 encoding polypeptide (See line 3, column 17, Xu et al., 1996).

With regard to tumor being resected following by an administration of a viral expression vector (claims 11-14, 26 of instant application), Xu et al. further teach the treatment of human non-small cell lung cancers *in vivo* is administered by bronchoscopy under topical or general anesthesia. To begin the procedure, *as much gross tumor as possible is resected endoscopically*. The residual tumor site is injected with the appropriate retroviral vector supernatant (Section 4.3.7), adenovirus suspension (Section 4.3.8) or plasmid vector-liposome complexes (Section 4.3.4 and 4.3.6) *at a volume of 5 ml to 10 ml* (See lines 7-11, column 31, Xu et al., 1996). Xu also teach retroviral vector at titer grater than 1 $X10^7$ colony-forming unit (cfu/ml) and such treatment can be repeated as many times as necessary (See lines 36-40, column 30, Xu et al., 1996).

With regard to administration of a viral expression vector into a natural or artificial body cavity, and frequency of administration (claims 16-18, and 36-37 of instant application), Xu et al. further cancer or tumor present in a *body cavity* such as in the eye, gastrointestinal tract, genitourinary tract (e.g., the urinary bladder), pulmonary and bronchial system and the like can receive a physiologically appropriate composition containing an effective concentration of active vectors via direct injection with a needle or via a catheter or other delivery tube placed into the cancer or tumor afflicted hollow organ (See lines 6-15, column 19, Xu et al., 1996). Xu also teach erosolization treatments for lung cancer with a tumor suppressor gene/pretein containing (purified protein or protein expressed from an expression vector) liposomes are administered to a patient for 30 minutes, *three times daily for two weeks*, with repetition as needed (See lines 33, column 31, and lines 21-23, column 32, Xu et al., 1996).

Treating human tumors via p53 gene therapy by administration of vector(s) expressing functional p53 was known in the art at the time of filing of instant application as evidenced by Fung et al., 2003. It is worth noting that a mutated p53 can be functional. For instance, alteration of an amino acid subject to regulation by phosphorylation status of p53 that would render the p53 being constitutively active and functional. In particular, Fung et al. taught (i) the reintroduction of a wild-type cDNA of p53 have been shown to partially restore normal growth regulation as the reintroduced genes induce growth arrest or retardation in many different tumor cell types (See lines 47-50 column 1, Fung et al., 2003), (ii) a method of treating malignant cell diseases in individuals comprising administration concurrently or consecutively into a proliferating cancer cell of a functional a functional mutated p53 gene (See lines 37-40, column

5, Fung et al., 2003), (iii) in gene therapy, it would be highly desirable to have mutant forms of the p53 gene, the protein of which is already active even without further modification.

It is worth noting that the inherent properties of p53 anticipate that expression of functional p53 would result in the induction of apoptosis in a tumor cell. For instance, the identification of the tumor suppressor gene p53 as a mediator of apoptosis was known in the art at the time of filing of instant application as evidenced by Donehower, 1994. In particular, Donehower taught that wild-type p53 induces apoptosis upon imbalance in growth regulatory signals (See Figure 1, page 162, Donehower, 1994), and the apoptotic role of p53 in tumor cells and in normal cells (See from the third column, page 163 to the end of page 194).

Thus, Xu et al. clearly anticipates claims 1-9, 11-14, 16-19, 26, 36, 37 and 146-150 of the instant invention.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 20, 27, and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (Xu et al., U.S. Patent 5,496,731 issued on March 5, 1996; listed as reference A12

in the IDS filed by applicant on Nov. 21, 2006) taken with Fung (U.S. Patent 6,590,086, issued July 8, 2003) and Roth et al. (Roth et al., U.S. Patent 6,797,702 issued on September 28, 2004).

Xu et al. teach broad-spectrum tumor suppressor genes, gene products and methods for *tumor suppressor gene therapy* (See title, Xu et al., 1996). The tumor suppressor genes taught by Xu et al. include **p53** (See section 1.3.3.3, column 5, Xu et al., 1996).

Xu et al., teach methods of treating a mammal having a disease or disorder characterized by abnormal cellular proliferation, such as a tumor or cancer and methods of treating abnormally proliferating cells, such as tumor or cancer cells (See abstract, Xu et al., 1996). In a more preferred embodiment the tumor or ***cancer cells are cells having no detectable genetic defect of a tumor suppressor gene --- a p53 gene*** (See lines 30-33 column 11, Xu et al., 2003) --- which reads on the limitation of a tumor cell expressing wild-type p53 recited in claim 1 of instant application ---; consistently, Xu et al. further teach that an advantage of the invention by Xu et al. is that *the methods and products herein disclosed* (which reads on expressing functional p53 for treating tumor recited in claim 1 of instant application) *can be used for therapeutic treating* ***tumors having no specific tumor suppressor gene defects***, which provides a significant advantage over previous techniques for human tumor suppressor gene therapy (See lines 22-27, column 15, Xu et al., 1996). Moreover, Xu et al. teach the ***human*** *bladder cancer* represents an ideal model for practicing tumor suppressor gene therapy of solid tumors (See lines 1-2, column 30, Xu et al., 2003), and the treatment of ***human*** *non-small cell lung cancers in vivo* (See lines 64-65, column 30, Xu et al., 1996).

With regard to various tumors (claims 2-5 of instant application), Xu et al. teach benign and malignant tumor (See line 50-51, column 11, Xu et al., 1996), lung carcinoma (line 35, column 11, Xu et al., 1996), and various sarcomas (See Table 1, column 15, Xu et al., 1996).

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With regard to viral expression construct (claims 6-9, 19 of instant application), Xu et al., teach expression vectors compatible with mammalian host cells for use in genetic therapy of tumor or cancer cells, include, but are not limited to: plasmids, retroviral vectors, adenovirus vectors, herpes viral vectors, and non-replicative avipox viruses, as disclosed, for example, by U.S. Pat. No. 5,174,993 (See last paragraph, column 16, Xu et al., 1996); and an adenovirus type 5 (Ad5) deletion mutant, Ad-d1324, and a plasmid, pTG5955 (Rosenfeld, M. A., et al., Cell, 1992, 68:143-155) are used to construct an adenovirus vector able to infect mammalian cells and express a tumor suppressor protein under the control of the adenovirus type 2 (Ad2) major late promoter, the CMV promoter, the β-actin promoter or any other effective promoter (See lines 20-27, column 17, Xu et al., 1996). It is noted that an adenovirus type 5(Ad5) deletion mutant harbors deletions at E1 and E3 regions. It is also noted that regarding the p53-encoding ploynucleotide being tagged so that expression of p53 from said expression vector can be detected (claim 19 of instant application), the limitation reads on the selection of the

expression vector bearing neo gene, which is indirectly tagged to the p53 encoding polypeptide (See line 3, column 17, Xu et al., 1996).

With regard to tumor being resected following by an administration of a viral expression vector (claims 11-14, 26 of instant application), Xu et al. further teach the treatment of human non-small cell lung cancers *in vivo* is administered by bronchoscopy under topical or general anesthesia. To begin the procedure, *as much gross tumor as possible is resected endoscopically*. The residual tumor site is injected with the appropriate retroviral vector supernatant (Section 4.3.7), adenovirus suspension (Section 4.3.8) or plasmid vector-liposome complexes (Section 4.3.4 and 4.3.6) *at a volume of 5 ml to 10 ml* (See lines 7-11, column 31, Xu et al., 1996). Xu also teach retroviral vector at titer grater than 1 $X10^7$ colony-forming unit (cfu/ml) and such treatment can be repeated as many times as necessary (See lines 36-40, column 30, Xu et.al., 1996).

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administered to a patient for 30 minutes, *three times daily for two weeks*, with repetition as needed (See lines 33, column 31, and lines 21-23, column 32, Xu et al., 1996).

Treating human tumors via p53 gene therapy by administration of vector(s) expressing functional p53 was known in the art at the time of filing of instant application as evidenced by Fung et al., 2003. It is worth noting that a mutated p53 can be functional. For instance, alteration of an amino acid subject to regulation by phosphorylation status of p53 that would render the p53 being constitutively active and functional. In particular, Fung et al. taught (i) the reintroduction of a wild-type cDNA of p53 have been shown to partially restore normal growth regulation as the reintroduced genes induce growth arrest or retardation in many different tumor cell types (See lines 47-50 column 1, Fung et al., 2003), (ii) a method of treating malignant cell diseases in individuals comprising administration concurrently or consecutively into a proliferating cancer cell of a functional a functional mutated p53 gene (See lines 37-40, column 5, Fung et al., 2003), (iii) in gene therapy, it would be highly desirable to have mutant forms of the p53 gene, the protein of which is already active even without further modification.

It is worth noting that the inherent properties of p53 anticipate that expression of functional p53 would result in the induction of apoptosis in a tumor cell. For instance, the identification of the tumor suppressor gene p53 as a mediator of apoptosis was known in the art at the time of filing of instant application as evidenced by Donehower, 1994. In particular, Donehower taught that wild-type p53 induces apoptosis upon imbalance in growth regulatory signals (See Figure 1, page 162, Donehower, 1994), and the apoptotic role of p53 in tumor cells and in normal cells (See from the third column, page 163 to the end of page 194).

However, Xu et al. does not teach (i) a method of inhibiting growth of a tumor comprising expressing functional p53 from a expression vector and contacting said tumor with *a DNA damaging agent* (claims 28-32 of instant application), (ii) p53-encoding polynucleotide is epitope tagged (claim 20 of instant application), and (iii) multiple injections of expression construct comprise about 0.1.0.5 ml volumes spaced about 1 cm apart (claim 27 of instant application).

At the time the claimed invention was made, the use of tumor suppressor genes in combination with a DNA damaging agent to kill cancerous cells was known in the art. For instance, Roth et al. teach method and compositions comprising a DNA damaging agents and p53 (See title, Roth et al., 2004). More specifically, Roth et al. teach (i) The *DNA damaging agents* or factors are defined as any chemical compound or treatment method that induces DNA damage when applied to a cell. Such agents and factors include radiation and waves that induce DNA damage, such as, γ-irradiation, X-rays, UV-irradiation, microwaves, electronic emissions, and the like, (ii) A variety of chemical compounds, also described as "chemotherapeutic agents", function to induce DNA damage, all of which are intended to be of use in the combined treatment methods disclosed herein. Chemotherapeutic agents contemplated to be of use, including, e.g., adriamycin, 5-fluorouracil (5FU), etoposide (VP-16), camptothecin, actinomycin-D, mitomycin C, cisplatin (CDDP), and even hydrogen peroxide, (iii) the invention also encompasses the use of a combination of one or more DNA damaging agents, whether radiation-based or actual compounds, such as the use of X-rays with cisplatin or the use of cisplatin with etoposide, and (iv) in certain embodiments, the use of cisplatin in combination

with a p53 protein or gene is particularly preferred as this compound (See bridging paragraph, columns 4-4, Roth et al., 2004).

Furthermore, with regard to claim 27 of instant application, Roth et al. teach 200 μl of medium containing Ad-p53 (10^8 PFU/ml) was injected into tumors with a diameter of 5 to 6 mm, and intratumoral injection (100 μl) and peritumoral injection in two opposite sites (50 μl each) were performed (See lines 57-62, column 12, Fig 13A legend, Roth et al., 2004). With regard to claim 27 of instant application, Roth et al., teach expression of p53 from Ad5CMV-p53 with is tagged with the epitope of SV40 early polyadenylation signal (See Fig. 1, Roth et al., 2004), and the exogenously expressed p53 from Ad5CMV-p53 is distinct from endogenously expressed p53 from human lung cancer cells (See lines 13-18, column 18, Roth et al., 2004).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to modify the method of inhibiting growth of a tumor cell expressing wild-type p53 in a human subject, and administration of p53 expressing viral vector for the suppression of tumor growth by the teachings of Xu et al. and combined with methods and compositions of comprising DNA damaging agent and p53, multiple injections of the compositions, and differentiation of exogenous versus endogenous p53 by epitope tagging, by the teachings of Roth et al., in order to achieve the goal of developing a method for inhibiting growth of tumor cell expressing wild-type p53 comprising administering a viral expression vector expressing a functional p53 and contacting the tumor with a DNA damaging agent.

One having ordinary skill in the art would have been motivated to combine the teachings of Xu et al. and Roth et al., because exposure of a tumor to a DNA damaging agent would

facilitate the induction of p53-mediated apoptosis, and thereby inhibiting tumor growth, as taught by Roth et al.; accordingly, the combination of p53 gene therapy with a DNA damaging agent would enhance the therapeutic effects of expression of functional p53 in inhibiting tumor growth by a mechanism involving p53-mediated apoptosis.

There would have been a reasonable expectation of success given (i) established role of functional p53 in inhibiting human tumor growth by the teachings of Xu et al. and Roth et al., and (ii) the improved therapeutic compositions fro use in killing cancer cells by combining the effects of a tumor suppressor gene or protein and a DNA damaging agent or factor, by the teachings of Rothe et al., 2004

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

5. Claims 1-9, 11-14, 16-19, 26, 36, 37, and 146-150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (Xu et al., U.S. Patent 5,496,731 issued on March 5, 1996; listed as reference A12 in the IDS filed by applicant on Nov. 21, 2006) taken with Zhang et al. (Zhang et al., U.S. Patent 6,143,290 issued on Nov 7, 2000; listed as reference A22 in the IDS filed by applicant on Nov. 21, 2006) and Donehower, 1994 (Tumor suppressor gene p53 and apoptosis, *The Cancer Bulletin* 46: 161-166, 1994; listed as reference C89 in the IDS filed by applicant on Nov. 21, 2006).

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be *directly injected into a target cancer or tumor tissue* by a needle in amounts effective to treat the tumor cells of the target tissue.

With regard to viral expression construct (claims 6-9, 19 of instant application), Xu et al., teach expression vectors compatible with mammalian host cells for use in genetic therapy of tumor or cancer cells, include, but are not limited to: plasmids, retroviral vectors, adenovirus vectors, herpes viral vectors, and non-replicative avipox viruses, as disclosed, for example, by U.S. Pat. No. 5,174,993 (See last paragraph, column 16, Xu et al., 1996); and an adenovirus type 5 (Ad5) deletion mutant, Ad-d1324, and a plasmid, pTG5955 (Rosenfeld, M. A., et al., Cell, 1992, 68:143-155) are used to construct an adenovirus vector able to infect mammalian cells and express a tumor suppressor protein under the control of the adenovirus type 2 (Ad2) major late promoter, the CMV promoter, the β-actin promoter or any other effective promoter (See lines 20-27, column 17, Xu et al., 1996). It is noted that an adenovirus type 5(Ad5) deletion mutant harbors deletions at E1 and E3 regions. It is also noted that regarding the p53-encoding ploynucleotide being tagged so that expression of p53 from said expression vector can be detected (claim 19 of instant application), the limitation reads on the selection of the expression vector bearing neo gene, which is indirectly tagged to the p53 encoding polypeptide (See line 3, column 17, Xu et al., 1996).

With regard to tumor being resected following by an administration of a viral expression vector (claims 11-14, 26 of instant application), Xu et al. further teach the treatment of human non-small cell lung cancers *in vivo* is administered by bronchoscopy under topical or general anesthesia. To begin the procedure, *as much gross tumor as possible is resected endoscopically*. The residual tumor site is injected with the appropriate retroviral vector

supernatant (Section 4.3.7), adenovirus suspension (Section 4.3.8) or plasmid vector-liposome complexes (Section 4.3.4 and 4.3.6) *at a volume of 5 ml to 10 ml* (See lines 7-11, column 31, Xu et al., 1996). Xu also teach retroviral vector at titer grater than 1 $X10^7$ colony-forming unit (cfu/ml) and such treatment can be repeated as many times as necessary (See lines 36-40, column 30, Xu et al., 1996).

With regard to administration of a viral expression vector into a natural or artificial body cavity, and frequency of administration (claims 16-18, and 36-37 of instant application), Xu et al. further cancer or tumor present in a *body cavity* such as in the eye, gastrointestinal tract, genitourinary tract (e.g., the urinary bladder), pulmonary and bronchial system and the like can receive a physiologically appropriate composition containing an effective concentration of active vectors via direct injection with a needle or via a catheter or other delivery tube placed into the cancer or tumor afflicted hollow organ (See lines 6-15, column 19, Xu et al., 1996). Xu also teach erosolization treatments for lung cancer with a tumor suppressor gene/protein containing (purified protein or protein expressed from an expression vector) liposomes are administered to a patient for 30 minutes, *three times daily for two weeks*, with repetition as needed (See lines 33, column 31, and lines 21-23, column 32, Xu et al., 1996).

It is worth noting that the inherent properties of p53 anticipate that expression of functional p53 would result in the induction of apoptosis in a tumor cell. For instance, the identification of the tumor suppressor gene p53 as a mediator of apoptosis was known in the art at the time of filing of instant application as evidenced by Donehower, 1994. In particular, Donehower taught that wild-type p53 induces apoptosis upon imbalance in growth regulatory

signals (See Figure 1, page 162, Donehower, 1994), and the apoptotic role of p53 in tumor cells and in normal cells (See from the third column, page 163 to the end of page 194).

However, even though the teachings by Xu et al. read on administration of a viral vector expressing wild type p53 in a tumor cell in human already expressing wild type p53, Xu et al. does not *explicitly* teach administration of a viral vector expressing wild type p53 in a tumor cell (claim 1, 146 of instant application).

At the time the claimed invention was made, the use of expressing of wild-type p53 from a viral vector in inhibiting tumor growth was known in the art. For instance, Zhang et al. 2000 teach tumor regression by adenovirus expression of wild-type p53. (See title, Roth et al., 2000). More specifically, Zhang et al. 2000 teach simplified and efficient methods for preparing recombinant adenovirus using liposome-mediated cotransfection and the direct observation of a cytopathic effect (CPE) in the *transfected cells*. Zhang et al. 2000 also disclosed the compositions and methods involving novel p53 adenovirus constructs, including methods for restoring p53 function and tumor suppression in cells and animals having abnormal p53 (See abstract, Zhang et al. 2000).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to modify the method of inhibiting growth of a tumor cell expressing wild-type p53 in a human subject by the teachings of Xu et al. and combined with the method of administration of p53 expressing viral vector for the suppression of tumor growth in the transfected tumor cells, by the teachings of Zhang et al., in order to achieve the goal of developing a method for inhibiting growth of tumor cell expressing wild-type p53 comprising administering a viral expression vector expressing a functional p53 in a human tumor cell.

One having ordinary skill in the art would have been motivated to combine the teachings of Xu et al. and Zhang et al., because the therapeutic effect of expressing wild type p53 from a viral vector *in vitro* (in transfected tumor cells) by the teachings of Zhang et al. and the method of inhibiting growth of a tumor cell expressing wild-type p53 *in vivo* (in a human subject) by expressing functional p53, by the teachings of Xu et al. in order to achieve the goal of a method of inhibiting growth of a tumor cell expressing wild-type p53 in a human subject by expressing functional p53 from a viral expression construct.

There would have been a reasonable expectation of success given (i) established the role of functional p53 in inhibiting human tumor growth by the teachings of Xu et al., including the published prior arts cited by Xu et al. and (ii) the successful demonstration of the therapeutic effect (tumor regression) via expressing wild type p53 from a viral vector *in vitro* (in transfected tumor cells) by the teachings of Zhang et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In reLongi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-14, 16-20, 26-32, 36, 37 and 146-150 are provisionally rejected under the judicially created doctrine of double patenting over claims 26, **29**, 58, **89** of copending Application No. 09/968,958.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In reBerg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). In the instant case, the method set forth in claim 1 of the instant application is essentially the same as that set forth in claims 29 and 58 of'958. Further, it is noted that claim 26 of application '958 encompasses essentially the same invention as encompassed by claims 1 and 146 of '033. Dependent claims in each application set forth specific types and amounts of vectors, specific types of cancers, and specific times of

administration that set forth inventions, which are essentially the same in breadth between both applications.

Applicant is advised that should claim 1 be found allowable, claim146 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In the instant case, simply indicating the mechanism on how the method works does not distinguish the claimed method from that set forth in claim 1 because the inherent properties of p53 anticipate that the administration of p53 will inhibit growth of a tumor cell by inducing apoptosis in a tumor cell.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

7. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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SUPERVISORY PATENT EXAMINER
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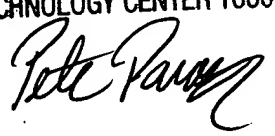

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